Levetiracetam monotherapy for seizure control in an HIV population

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Introduction

Seizures represent a manifestation of nervous system involvement that is common among patients infected with human immunodeficiency virus (HIV), with a reported frequency rate ranging from 3-11% (1,2). This rate is higher than the 1-2% frequency reported in the general population (3). In patients infected with HIV, the seizure recurrence rate can be as high as 70% (4), warranting early initiation of anticonvulsants. Diagnosis and management of seizures in this population can be challenging and quite different from non-HIV-infected patients. The seizures can be pre-existing or new-onset in nature; in certain instances, seizures can be the initial manifestation of HIV. Etiology, when identifiable, is often associated with intracranial mass lesions, including toxoplasmosis and primary central nervous system lymphoma (5). Given the large number of antiretroviral medications that are utilized by the HIV-infected population, the use of monotherapy for seizure control has obvious potential value. Certain factors must be considered, however, when antiretrovirals and anticonvulsants are administered concomitantly. A thorough understanding of each agent's pharmacokinetic profiles, including protein binding, route of metabolism, and loading/titration schedules, must be considered to avoid potential drug-drug interactions and preserve the efficacy and safety of both agents. Levetiracetam (LEV), an anticonvulsant approved as adjunctive therapy for partial onset seizures in patients 4 years of age and older, has many pharmacokinetic properties which make it an ideal agent for use in the HIV population. In an effort to consider a future study of LEV monotherapy for seizure control in the HIV population, we reviewed our experience with its use in our HIV cohort.

Methodology

A retrospective search was performed utilizing electronic medical records from the author's complete cohort of patients diagnosed with HIV, dating back to 2000. Search terms included the words "Keppra" or "levetiracetam." Inclusion criteria consisted of:

1. Cases during which LEV had been used as monotherapy for seizure control, and
2. Cases having a known follow-up period.

In addition, reasoning for use of LEV in this manner was identified and noted. All cases during which LEV was considered as monotherapy were reviewed; if not used, reasoning was documented. Follow-up was performed through the patient's treating neurologist and/or the patient him/herself.

Case Reports

Case 1

A 34-year-old HIV-infected female with diagnosis of partial complex seizures due to HIV encephalitis, HIV myelopathy and HIV neuropathy had been very difficult to control in terms of seizure frequency. Gabapentin 200 mg BID was added to her phenytoin 300 mg BID, which resulted in a decrease in seizure frequency. The patient's cognitive status was abnormal and included inattention, poor recall and non-compliance. After a flurry of partial complex seizures with some element of secondary generalization in relation to non-compliance, LEV was started at an initial dose of 500 mg BID; gabapentin and phenytoin were subsequently withdrawn. She immediately became seizure free and has remained so. Her mental status also normalized, suggesting sub-clinical seizure

activity as its etiology. She has been clinically seizure free for 18 months on LEV monotherapy without any adverse effects.

Case 2
A 44-year-old HIV-infected male with seizures of uncertain etiology (although presumably due to HIV encephalitis) had been accepted into a highly active antiretroviral study. However, the patient was maintained on phenytoin and had been seizure free. Phenytoin was an exclusion from the drug study. The patient was switched on one day to LEV 500 mg BID and then arbitrarily increased to 750 mg BID two weeks later. Initially the patient experienced some drowsiness which passed; otherwise, there were no adverse effects and the patient has been entirely seizure free.

Case 3
A 42-year-old HIV-infected female with a history of poorly controlled seizures of a partial complex nature (etiology uncertain, although presumably due to HIV encephalitis) presented to the ED with a seizure. LEV was initiated at 500 mg BID (added to current therapy, which included phenytoin and gabapentin) and was increased to 750 mg BID. After a period of being seizure free, the gabapentin was discontinued and the phenytoin was tapered. The patient developed an ischemic stroke manifesting as aphasia shortly thereafter.

Case 4
A 33-year-old female with a long history of secondarily generalized seizures had a recurrence of seizures during the course of her HIV infection. Clinical workup, including MRI and spinal fluid, was negative for etiology. LEV was initiated at 500 mg BID and increased to 750 mg BID. The patient has been seizure free for over 12 months, exhibiting no adverse effects or untoward reactions to LEV.

Patients with the following clinical conditions were considered for LEV monotherapy, but it was not utilized due to the patients' inability to obtain the medication:

1. Patients on valproate monotherapy.
2. Patients on phenytoin or carbamazepine monotherapy with poor antiretroviral status.
3. Any new-onset partial seizure with or without secondary generalization.

Discussion
Characteristics of the antiretroviral drug regimen typically employed in HIV-infected patients can be a limiting factor when an anticonvulsant is required for seizure control. Most antiretroviral agents are metabolized by the cytochrome P450 system, as are many anticonvulsants. Concomitant antiretroviral-anticonvulsant use has been associated with both increases and decreases in anticonvulsant concentrations (6), loss of viral suppression (6), and decreased concentrations of antiretrovirals (7). Valproic acid is associated with an increase in HIV viral replication *in vitro* and may pose a risk of hepatic failure when used concomitantly with antiretrovirals (8). In addition, anticonvulsants can result in undesirable and potentially dangerous adverse effects; Holtzman et al. reported hypersensitivity reactions in 14% of HIV-infected patients taking phenytoin (9).

Levetiracetam, a pyrrolidine derivative, is a novel anticonvulsant that is potentially useful in treating seizures in HIV-infected patients. The pharmacokinetic profile of LEV is characterized by minimal protein binding (<10%) and no metabolism by the cytochrome P450 system (10,11), which make it favorable for treating seizures in this population due to low risk of drug-drug interactions. Older anticonvulsants are heavily protein-bound and are almost exclusively dependent on the cytochrome P450 system for metabolism. LEV can be taken as tablets or as oral solution, which may improve gastrointestinal absorption as well as compliance in the HIV population.

Double-blind, multicenter, placebo-controlled studies of LEV in the treatment of partial onset seizures have shown response rates (≥50% reduction in seizure frequency) of 20.8-39.6% at doses ranging from 1000-3000 mg/day (12). The most common adverse events in these studies were asthenia, dizziness, infection (common cold) and somnolence. LEV requires no loading or titration and can be initiated at an effective dose. Additionally, LEV displays linear pharmacokinetics over a wide dose range (Table 1). In a study of patients on multidrug antiretroviral therapy, LEV monotherapy 1000-1500 mg was not associated with interactions with antiretroviral efficacy and was well tolerated (13). Effective seizure control was maintained in all subjects.

Table 1. Summary of pharmacokinetic parameters of levetiracetam in healthy adults.

	Dose Level					**Package Insert Value**
Parameter (unit)	**500 mg**	**1000 mg**	**2000 mg**	**3500 mg**	**5000 mg**	
C_{max} (μg/mL)	10.6	28.2	50.1	97.0	123.4	-
T_{max} (hours)	1.0	1.3	0.8	0.8	0.6	Approx.1
$AUC_{0-\infty}$ (μg • h /mL)	110.2	206.9	438.8	712.3	1019	-
$t_{½}$ (hours)	6.9	6.4	7.1	6.6	6.5	7 ± 1

Summary

The prevalence of seizures is increased in the HIV population. Pharmacokinetic properties limit choices for seizure control in these patients due to cytochrome P450 metabolism and extensive protein binding of antiretrovirals and anticonvulsants. The number of antiretroviral agents typically employed in HIV management highlights the potential value of utilizing a single anticonvulsant for seizure control. Our case report series showed the therapeutic value of LEV monotherapy in the treatment of seizures in HIV patients. The minimal protein binding and lack of cytochrome P450 metabolism make LEV unlikely to produce clinically significant drug-drug interactions with antiretroviral agents. LEV has proven efficacy in partial onset seizures and, although not indicated for use as monotherapy, has shown favorable results when used in this manner. In a previous study of HIV patients, LEV was efficient in seizure reduction and showed no interference with antiretroviral agents, while being well tolerated. We believe our results warrant a need for a larger, prospective study to examine LEV monotherapy for partial onset seizures in the HIV population.

References

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Recommended readings:
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